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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/687,402	10/16/2003	Jaya Sivaswami Tyagi	AP35478 066123.0125	8618
21003 7590 10/23/2007 BAKER BOTTS L.L.P. 30 ROCKEFELLER PLAZA 44TH FLOOR NEW YORK, NY 10112-4498			EXAMINER FERNANDEZ, SUSAN EMILY	
			ART UNIT	PAPER NUMBER
			1651	
			NOTIFICATION DATE	DELIVERY MODE
			10/23/2007	ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DLNYDOCKET@BAKERBOTTS.COM

<b>Office Action Summary</b>	<b>Application No.</b> 10/687,402	<b>Applicant(s)</b> TYAGI ET AL.	
	<b>Examiner</b> Susan E. Fernandez	<b>Art Unit</b> 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 05 July 2007.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 22-37 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 22-37 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### DETAILED ACTION

The amendment filed July 5, 2007, has been received and entered.

Claims 1-21 are canceled. Claims 22-37 are pending.

Applicant's election with traverse of the species wherein DevS<sub>578</sub> is the DevS derivative, Rv2027<sub>194</sub> is the Rv2027 derivative, and DevRN<sub>145</sub> is the DevR derivative, in the reply filed December 9, 2004, is acknowledged and applies to the new claims (claims 24, 26, 28, 29, 32, 34, 36, and 37).

Claims 22-37 are examined on the merits to the extent they read on the elected subject matter.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification as filed contains no limitations of the determination of the drug potential of the test compound wherein the potency of the drug is inversely proportional to "the degree of phosphotransfer" from "phosphorylated DevS to DevR" (claim 22), "phosphorylated

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single domain derivative of DevS to DevR” (claim 23), “phosphorylated DevS to a single domain derivative of DevR” (claim 25), “phosphorylated single domain derivative of DevS to a single domain derivative of DevR” (claim 27), “phosphorylated Rv2027c to DevR” (claim 30), “phosphorylated single domain derivative of Rv2027c to DevR” (claim 31), “phosphorylated Rv2027c to a single domain derivative of DevR” (claim 33), or “phosphorylated single domain derivative of Rv2027c to a single domain derivative of DevR” (claim 35). Instead, the disclosure indicates that the potency of the drug is inversely proportional to “the degree of phosphotransfer-based dephosphorylation of DevR and its single domain derivative” (page 25, paragraph [0059]), thus implying phosphotransfer from phosphorylated DevR, where the recipient(s) is not disclosed. The rate of dephosphorylation of phosphorylated species of species of DevS and Rv2027c do not speak to the degree of phosphotransfer to DevR, nor does Figure 9 or any reference to Figure 9 correlate phosphotransfer from DevS or Rv2027c to DevR to determinations of drug potency.

Additionally, the specification does not disclose the determination of the drug potential of the test compound wherein the potency of the drug is inversely proportional to “the degree of loss of phosphate-associated radioactivity” from “DevS or DevR in a reaction containing DevS and DevR” (claim 22), “a single domain derivative of DevS or DevR in a reaction containing a single domain derivative of DevS and DevR” (claim 23), “DevS or a single domain derivative of DevR in a reaction containing DevS and a single domain derivative of DevR” (claim 25), “single domain derivative of DevS or a single domain derivative of DevR in a reaction containing a single domain derivative of DevS and a single domain derivative of DevR” (claim 27), “Rv2027c or DevR in a reaction containing Rv2027c and DevR” (claim 30), “a single domain

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derivative of Rv2027c or DevR in a reaction containing a single domain derivative of Rv2027c and DevR” (claim 31), “Rv2027c or a single domain derivative of DevR in a reaction containing Rv2027c and a single domain derivative of DevR” (claim 33), or “single domain derivative of Rv2027c or a single domain derivative of DevR in a reaction containing a single domain derivative of Rv2027c and a single domain derivative of DevR” (claim 35). Though paragraph [0178] indicates that in screening of inhibitors, “presence of a true inhibitor will not lead to reduction of retention of radioactivity on the filter,” the specification does not specify that there is a clear relationship between drug potential and loss of phosphate-associated radioactivity. There is no teaching that any reduction of retention of radioactivity on the filter determines anti-mycobacterial drug potential. In sum, because the specification as filed fails to provide clear support for the new claim language, a new matter rejection is clearly proper.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

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invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoch et al. (US Patent 6,043,045) in view of Dasgupta et al. (2000, *Tubercle and Lung Disease*, 80(3): 141-159).

Hoch et al. discloses a method for identifying new antibiotic, antibacterial, or antimicrobial agents by inhibition of bacterial two-component systems. Specifically, agents are sought that cause the "inhibition of either the autophosphorylation or the subsequent phosphotransfer" (column 2, lines 16-23). Furthermore, the conventional use of SDS-PAGE to assay two-component systems is described (column 2, lines 24-35), where autoradiographic analysis is used. Hoch et al. provides a high-throughput screening assay for histidine protein kinase for agent identification (column 22, lines 16-24), as described in Example 1 starting at lines 30 of column 15. In this high-throughput screening assay, the histidine protein kinase (KinA) and its substrate (SpoOF) are expressed in *E.coli* and purified (column 15, lines 45-47). This can be considered the overexpression of the histidine protein kinase. This high-throughput screening assay measures the extent of phosphorylation of the substrate and the radioactivity remaining on a resin (column 2, lines 50-53 and column 17, lines 43-45) following SDS-PAGE analysis.

Hoch et al. does not expressly disclose the use of their methods for inhibition of DevR-DevS or DevR-Rv2027c and its homologues nor does it disclose the identification of anti-tuberculosis and anti-mycobacterial compounds. Additionally, Hoch et al. does not disclose the

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relation between the potency of a drug and the degree of phosphotransfer and loss of phosphate-associated radioactivity.

Dasgupta et al. discloses the DevR-DevS two-component system in mycobacteria, specifically *M. tuberculosis*, as well as the homology of Rv2027c with DevS. It is obvious that DevS<sub>578</sub>, Rv2027<sub>194</sub>, and DevRN<sub>145</sub> would share common characteristics with DevS, Rv2027 and DevR respectively because, as evidenced by Dasgupta (Figure 3, page 148 and Figure 5, page 150), the claimed portions each contain the catalytic site of the molecules, based on the size of the transcripts disclosed in the reference.

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to apply the methods of Hoch et al. to the DevR-DevS and the known homolog of DevR-Rv2027c as described in Dasgupta et al. The DevR-DevS and DevR-Rv2027c systems both comprise a histidine protein kinase (DevS or Rv2027c), thus being appropriate as a target of the Hoch invention. By applying the Hoch invention to the DevR-DevS system, it would be obvious that an agent positively identified could be used for tuberculosis or other diseases caused by mycobacteria.

One of ordinary skill in the art would have been motivated to do this because Dasgupta et al. concludes that "the devR-devS two-component system may thus serve as a novel target for anti-tubercular therapy" (page 158, second paragraph). Tuberculosis is a critical issue, so there is a high incentive to develop or determine compounds for its treatment. There would have been a reasonable expectation of success that the Hoch invention could be used for bacteria such as *M. tuberculosis* that have DevR-DevS and/or DevR-Rv2027c and its homologues based on the fact that Hoch's assay techniques are disclosed as measuring the same reactions catalyzed by

Dasgupta's tuberculosis phosphorylases. Finally, it would have been obvious to have expected the same correlation between drug potency and phosphotransfer and radioactivity as recited in claim 1, section c. The degree of phosphotransfer and loss of phosphate-associated radioactivity would have inherently occurred when using the histidine protein kinase system of the claims, as the Hoch reference and the claims under examination use the same processes. In sum, the system of Dasgupta et al. would appear to be just the kind of system that Hoch et al. suggests their methods are applicable for. A holding of obviousness is therefore proper.

### *Response to Arguments*

Applicant's arguments filed July 5, 2007, have been fully considered but they are not persuasive. In arguing against the new matter rejections, the applicant asserts that the specification clearly identifies phosphotransfer from DevS or Rv2027c to DevR as a point where drug intervention is possible, pointing out that paragraph [0092] in the specification provides support. The following recitation is highlighted in paragraph [0092]: "Successful biochemical reconstitution of these two-component systems has provided the means for the development of rapid high-throughput assays to screen compound or drug libraries for lead molecules that could interfere with these signal transduction pathways." It is respectfully noted that paragraph [0092], including the above highlighted sentence, does not indicate or suggest that the potency of a drug is *inversely proportional* to the degree of phosphotransfer from the phosphorylated sensor (DevS/Rv2027c) to DevR. Furthermore, the applicant points to paragraph [0020] and Figures 9 and 10 of the specification, noting that genetic DevR disruption is functionally equivalent to the claimed inhibition of phosphotransfer. However, this statement is not made in the specification,



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and paragraph [0020] is drawn to blocking DevR and DevS/Rv2027c activity, with no mention of phosphotransfer or that the blocking of the activities is as a result of the effects of phosphotransfer.

With respect to Figures 9 and 10, it is respectfully noted that it is unclear that dephosphorylation of DevS or Rv2027c indeed correlates with phosphotransfer to DevR. Applicant alleges that the specification clearly identifies that DevS or equivalents will remain phosphorylated for up to four hours unless presented with the opportunity to transfer the phosphate to DevR or equivalents, but the applicant does not cite support in the specification for this statement. Furthermore, it is unclear how this relates as support for the claim recitation that the degree of inhibition of phosphotransfer from DevS or equivalents to DevR or equivalents correlates to drug potency. It is also unclear how Figure 9 demonstrates that there is a concomitant increase in phosphorylation of DevR during dephosphorylation.

Moreover, it is unclear the specification teaches that the inhibition of phosphotransfer from DevS or Rv2027c results in inhibition of DevR or even mirrors the inhibition of DevR, and it is not apparent that the specification teaches that this phosphotransfer is to DevR.

Additionally, the previous office action asserts that the specification does not disclose that the potency of a test compound is inversely proportional to the degree of loss of phosphate-associated radioactivity from DevS or DevR in a reaction containing DevS and DevR or their equivalents. The applicant argues that given the teachings of paragraph [178] and Figures 14A and 14B, the extent to which any drug would inhibit loss of phosphate-associated radioactivity would essentially be equivalent to a situation where DevR had been rendered non-functional. It is unclear how Figures 14A and 14B demonstrate this. Moreover, there is no indication in

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paragraph [178] that there is a direct relationship between degree of loss of phosphate-associated radioactivity and drug potency. It only speaks to the situation where there is a true inhibitor, and thus only to one extreme of drug potency.

Finally, in the arguments regarding the rejections of the claims over Hoch et al. and Dasgupta et al., the applicant argues that a prima facie case of obviousness had not been established. The applicant argues that Dasgupta et al. does not provide any support for arguing that inhibition of phosphotransfer correlates with drug potency. However, the primary reference teaches that antimicrobial agents can be identified by inhibition of bacterial two-component systems, thus the substitution of the Dasgupta bacterial two-component system would have been obvious to achieve the predictable result of identifying antimicrobial agents. Hoch et al. indeed teaches the measurement of the extent of phosphorylation and radioactivity. Additionally, it is noted that KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, -- USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396). Thus, the rejections of record must be maintained.

No claims are allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO**

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MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan E. Fernandez whose telephone number is (571) 272-3444. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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